Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ITCH WORMER Plus XL Tablets for Dogs
Ezi-Wormer Plus XL Tablets for Dogs
TermaWorm Dog XL Tablets for Dogs 175/504/525 mg
VetUK XL Dog Wormer Tablets

Date Created: May 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	ITCH WORMER Plus XL Tablets for Dogs Ezi-Wormer Plus XL Tablets for Dogs TermaWorm XL Tablets for Dogs 175/504/525 mg VetUK XL Dog Wormer Tablets (504 mg pyrantel embonate, 175 mg Praziquantel, 525 mg Febantel)
Applicant	C&H Generics Limited c/o Michael Mc Evoy and Co. Seville House New Dock Street Galway Ireland
Active substance	504 mg pyrantel embonate 175 mg Praziquantel 525 mg Febantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	In adult dogs: Treatment of mixed infections by nematodes and cestodes of the following species **Nematodes:** **Ascarids:** *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms). **Hookworms:** *Uncinaria stenocephala*, *Ancylostoma caninum* (adults). **Whipworms:** *Trichuris vulpis* (adults). **Cestodes:** **Tapeworms:** *Echinococcus* species, *(E. granulosus, E. multilocularis), Taenia* species, *(T. hydatigena, T. pisiformis, T. taeniformis),*

	Dipylidium caninum (adult and immature forms).

MODULE 2

The Summary of Product Characteristics (SPC) for these products is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

Applications for these identical tablets were submitted under Article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC, for 'hybrid' products, as bioequivalence to a reference product cannot be demonstrated. The reference product was Drontal Plus Flavour Tablets for Dogs. The proposed products are additional tablet strengths to the Extranet/EziWormer/Quantilex/Rofectan Plus Tablets for Dogs already authorised in the UK. The formulation is also already authorised in the UK as the Cazitel/Prazitel/Quantilex/Strantel Plus XL Tablets for Dogs range. The indications for use are for the treatment of gastrointestinal roundworms and tapeworms in dogs. Roundworms: *Toxocara cati*, *Toxascaris leonina.* Tapeworms: *Dipylidium caninum, Taenia taeniaeformis*, *Echinococcus multilocularis.* The recommended dose rates are: 15mg/kg bodyweight febantel, 5 mg/kg pyrantel (equivalent to 14.4 mg/kg pyrantel embonate) and 5 mg/kg praziquantel.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain 175 mg praziquantel, 504 mg pyrantel and 525 mg febantel. The excipients for the core tablet are maize starch, microcrystalline cellulose, crospovidone, magnesium stearate and colloidal anhydrous silica. The excipients for the film coat are grilled meat flavour Opadry Complete Film Coating System 03F28415 White consisting of HPMC 2910 hypromellose (E464), macrogol/PEG 4000 (E1521), and titanium dioxide (E171).

The container/closure system consists of Blister packs made up of PVC/PE/PCTFE with 20µ hard tempered aluminium foil with 2 or 4 tablets per blister. The Blisters are packed into cartons containing either 2 or 4 tablets. (VetUK XL, ITCH WORMER Plus XL).

Blister packs made up of PVC/PE/PCTFE with 20µ hard tempered aluminium foil with 2, 4, 5, 6, 8, 10, 12, 14, 16, 18 or 20 tablets per blister.

The Blisters are packed into cartons containing either 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 40, 42, 44, 48, 50, 52, 56, 60, 64, 68, 70, 72, 76, 80, 84, 88, 92, 96, 98, 100, 104, 106, 108, 112, 116, 120, 140, 150, 180, 200, 204, 206, 208, 250, 280, 300, 500 or 1000 tablets. (Ezi-Wormer Plus XL, TermaWorm).

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a standard wet granulation/compression technique.

II.C. Control of Starting Materials

The active substances are praziquantel, pyrantel and febantel, established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. Suitable certificates of suitability and/or applicable alternative data were provided.

All excipients comply with appropriate Ph. Eur monographs, apart from the pork flavour, which is specified by a certificate of analysis and technical data sheet. Packaging materials comply with defined specifications.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, identification of active substances, weight, friability, hardness, moisture, dissolution, uniformity of dose and microbial purity.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Suitable retest data for the active substances were received.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 5 years VetUK XL.

Unused half tablets must be used within 14 days.

This veterinary medicinal product does not require any special storage conditions. Each time an unused half tablet is stored, it should be returned to the open blister space and inserted back into the cardboard box.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

These were 'hybrid' applications made in accordance with Article 13 (3) of Directive 2001/82/EC as amended, as bioequivalence to the reference product cannot be demonstrated. The applications were supported with regard to safety data by proprietary and published literature.

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Praziquantel

Praziquantel is a pyrazinoisoquinoline, which is active against schistosomes. Spastic paralysis of the musculature is thought to lead to a depolarising effect on the internal cellular structure, leading to breakdown of the function of the cell membrane of the target parasite.

Pyrantel

Pyrantel is an imidazothiazole with activity against nematodes. A cholinergic agonist, it acts by inducing a neuromuscular blockade within the target parasite.

Febantel

This active substance is a probenzimidazole with activity against nematodes. Metabolism to fenbendazole and oxfendazole propagates the destruction of the target parasite membrane and microtubule structure, and glucose metabolism, affecting the generation of ATP. [3]

Pharmacokinetics

Praziquantel

Praziquantel is rapidly and extensively absorbed in many species, including dogs. There is extensive first pass metabolism, with the main metabolites being hydroxylation products. Rapid elimination occurs via the bile, urine and gut mucosa.

Pyrantel

Pyrantel is slowly absorbed from the gut, having poor solubility in water. Much of the active substance therefore remains to exert activity within the large intestine.

[3] ATP – Adenosine triphosphate.

The majority of inactive metabolites arising from related process are expelled in the faeces. A portion of the drug is expelled unchanged.

Febantel

The applicant provided data relating to the active metabolite fenbendazole, (the other active metabolite being oxfendazole), as utilised in dogs. Large variations in metabolism are noted on the use of different dosing regimens. Elimination occurs almost completely, within 3 to 7days.

Pharmacokinetics of all three active substances used in combination

In studies in dogs, fenbendazole, praziquantel and pyrantel were rapidly metabolised. Data were presented which showed that use of the active substances together had a more beneficial effect that use of them alone. For all parameters, it can be assumed that the action of the three active substances in combination can be expected to be similar to the pharmacokinetic properties of the reference product.

Toxicological Studies

Single dose toxicity

All three active substances are generally considered to be of low toxicity. The oral LD_{50}[4] in the rabbit is approximately 1050mg/kg for praziquantel. Oral studies in dogs are limited by emesis, which may occur at 100 mg kg. No deaths were observed in a study providing animals with up to 400 mg/kg.

An LD_{50} of>5000 mg kg was observed in rats, and in dogs, >690 mg/kg. For febantel, an LD_{50} of 1250 mg/kg was observed in rabbits, and in dogs >10, 000 mg/kg.

Repeated dose toxicity

All three active substances were noted to have limited toxicity on repeated dose. The SPC and product literature carry suitable warnings. From CVMP[5] summary reports, the ADI of praziquantel was noted as being 0.02 mg/kg/day based on a NOEL of 20 mg/day in a sub-chronic dog study. For pyrantel, a 2 year dog study provided an ADI calculated from a NOEL of 3 mg/kg. An ADI of 7 µg/kg/bw/day for oxfendazole (the active metabolite of febantel), was seen in rats. This was based on a NOEL of 0.65 mg/kg/bw/day.

Reproductive toxicity, including teratogenicity

The effects of praziquantel in laboratory species have been extensively studied. Male and female rats have been shown to be essentially unaffected by doses of

[4] LD_{50} – Dose expected to be fatal to half a tested population.
[5] CVMP – Committee for Medicinal Products for Veterinary Use.

up to 300 mg/kg. There has been no effect seen on dogs given doses of up 26.8 mg/kg at significant stages of reproduction.

For pyrantel pamoate, no reproductive effects were seen on rats given up to 90 mg/kg/day up to weaning, or in rabbits given up to 90 mg/kg/day from days 7 to 17 of gestation. Some instances of resorption were observed. No teratogenic effects were observed in male and female dogs. Extensive data have not revealed any significant reproductive effects on dogs.

Febantel and the associated metabolite oxfendazole have been shown to be toxic to rats at doses of 50-100 mg/kg. In mares, given two times the recommended dose from 40 days before conception to 148 post-delivery, no genotoxic effects were observed. No evidence of teratogenicity has been found in dogs.

Mutagenicity

No significant mutagenic effects are associated with the three active substances.

Observations in Humans

No long-term adverse effects from the use of praziquantel have been documented as occurring in man. Metabolism is fast, with the major metabolites being quickly eliminated. Oral doses of up to 50 mg/kg are well tolerated in adults, with the therapeutic dose being normally 5 mg/kg bw single dose, or 3 x 25 mg/kg/bw for up to 3 days, or 50-60 mg/kg/bw for up to 15 days.

In man, pyrantel has been extensively used for many years, and is generally given as a pamoate salt at oral doses of 10-20 mg/kg/day for 1 to 3 days. Some gastro-intestinal, central nervous system and skin disturbances have been observed.

Neither febantel nor its metabolites are used in human medicine. The excipients are commonly used in medicinal products and are not expected to cause irritation. The SPC and product literature carry suitable warnings.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

In case of accidental ingestion, seek medical advice and show the package leaflet to the physician. In the interests of good hygiene, persons administering the tablets directly to the dog, or by adding them to the dog's food, should wash their hands afterwards.

Environmental Safety

The products are intended to be used in individual animals, provided to the animal directly or in food. It is therefore unlikely that the products will directly enter the environment. An environmental risk assessment ending at Phase I was acceptable.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant provided reference data for this section, as previously referred to in Section III.

A comparative dissolution study was provided in order to demonstrate parity between the previously authorised products and the proposed products. 0.1M HCL was used as the dissolution medium, and the product was tested at a variety of pH, 4.5, 6.8 and 7.5. The dissolution profiles were considered comparable, and the following conclusions were drawn:

- The reference product is a pro rata formulation of the proposed product. The reference product has been formulated to have the same active substances and excipients in the same ratio, as the authorised product, and,
- the proposed indications and the proposed doses for the individual active substances are the same for both products; and,
- the dissolution profile for both tablet strengths is comparable in all dissolution media for all active substances

Tolerance in the Target Species

The data for this section was previously assessed for the 'Plus XL' reference products. There was therefore no requirement to re-assess these data. The following justification is acceptable for comparison of reference and proposed products:

- the nature of this application (line extension application)

- the fact that Extronel/Ezi-Wormer/TermaWorm/VetUK XL has been formulated to have the same composition, pro rata, in terms of active substances and excipients, as the authorised products, Extronel/EziWormer/Quantilex/Rofectan Plus,

- the fact that the proposed conditions of use of Extronel/EziWormer/ TermaWorm/Vet UK XL are identical to those of

the authorised product, with the exception that Extronel/EziWormer/ TermaWorm/VetUK XL is intended for use in large
dogs (that is, no difference between products in terms of mg/kg dose of actives),

- *in vitro* dissolution profiles for both products are comparable in all dissolution media for all active substances indicating similar rate of release of active substances following ingestion, and

- the fact that Extronel/EziWormer/ TermaWorm /VetUK XL is not considered to pose an unacceptable risk to the target animal.

Resistance

These data were assessed for previously approved applications for the reference products, no additional changes were noted. The SPC and product literature carry suitable warnings.

IV.II. Clinical Documentation

As this was a line extension of the reference products, no additional data other than the comparative dissolution study were assessed for the proposed products.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)